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Relationship between blood alcohol concentration on admission and outcome in dimethoate organophosphorus self-poisoning

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Acute alcohol intoxication often complicates acute organophosphorus pesticide poisoning.
- No data are available on how alcohol intoxication affects outcome in acute organophosphorus pesticide poisoning.
- In particular, the relationships between plasma alcohol concentration and plasma organophosphorus concentration or outcome are unclear.

WHAT THIS STUDY ADDS

- Alcohol co-ingestion is associated with higher concentrations of the organophosphorus insecticide dimethoate, probably due to larger ingestions.
- The higher concentrations of dimethoate found with alcohol co-ingestion increase the risk of death in dimethoate poisoning. There was no detectable effect of the alcohol itself on outcome.
- Efforts to reduce deaths from insecticide self-poisoning may benefit from concurrent efforts to reduce alcohol consumption.

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AIMS

Many patients acutely poisoned with organophosphorus insecticides have co-ingested alcohol. Although clinical experience suggests that this makes management more difficult, the relationship between plasma concentration of alcohol and insecticide is unknown. We aimed to determine whether acute intoxication results in ingestion of larger quantities of insecticide in dimethoate self-poisoning and a worse clinical outcome.

METHODS

We set up a prospective study of acute dimethoate self-poisoning in Sri Lankan district hospitals. An admission plasma sample was analysed to identify the ingested insecticide; in patients with detectable dimethoate, plasma alcohol was measured.

RESULTS

Plasma from 37 of 72 (51.4%) dimethoate-poisoned patients had detectable alcohol {median concentration 1.10 g l⁻¹ [110 mg dl⁻¹] [interquartile range (IQR) 0.78–1.65]} a median of 3 h post ingestion. The median plasma dimethoate concentration was higher in patients who had ingested alcohol [479 µmol l⁻¹ (IQR 268–701) vs. 145 µmol l⁻¹ (IQR 25–337); *P* < 0.001]. Plasma dimethoate concentration was positively correlated with plasma alcohol (Spearman's *ρ* = 0.34; *P* = 0.0032). The median alcohol concentration was higher in the 21 patients who died compared with survivors (0.94 vs. 0.0 g l⁻¹, *P* = 0.018). Risk of death was greater amongst individuals who consumed alcohol [odds ratio (OR) 4.3, 95% confidence interval (CI) 1.2, 16.4]; this risk was abolished by controlling for dimethoate concentration (OR 0.3, 95% CI 0.0, 8.8), indicating that deaths were not due to the direct toxic effects of alcohol.

CONCLUSIONS

Alcohol co-ingestion is associated with higher plasma concentrations of dimethoate and increased risk of death. Larger studies are required to assess this finding's generalizability, since efforts to reduce deaths from self-poisoning may benefit from concurrent efforts to reduce alcohol consumption.

Introduction

Pesticide self-poisoning is a major global health problem, killing 250–350 000 people each year [1, 2]. Organophosphorus (OP) insecticide poisoning is a particularly severe problem, accounting for around two-thirds of deaths [3]. OP insecticides produce acetylcholinesterase inhibition, resulting in cholinergic overstimulation at autonomic, neuromuscular and central synapses. Death results from respiratory failure, sometimes complicated by distributive cardiovascular shock [4]. Current treatment options for OP poisoning are often ineffective [4], with case fatality commonly exceeding 20% [3]. The importance of co-ingestants in determining outcome in OP poisoning is not yet clear.

Many poisoning deaths in rural Asia occur in middle-aged men who have co-ingested alcohol [5–8]. Clinical experience suggests that alcohol intoxication makes management of OP insecticide-poisoned patients more difficult, possibly by exacerbating the suppressive effects of the OP on conscious level and respiratory drive. Chronic alcohol use probably causes additional difficulties [9]: tachycardia and delirium due to withdrawal complicating administration of atropine, and alcoholic myopathy increasing the risk of cardiac complications from atropine therapy.

Due to an impression that OP-poisoned patients with significant alcohol co-ingestion in our Sri Lankan cohort had a poor prognosis, we studied the effect of plasma alcohol concentration on admission on outcome. We chose patients poisoned by dimethoate since the plasma concentration of this OP has a clear relationship with outcome [10], unlike some other OPs such as chlorpyrifos [10]. We hypothesized that alcohol intoxication would increase the amount of insecticide drunk by an individual – reasons might include impairment of ability to judge the quantity of poison ingested, dulled taste sensation, and disinhibition – and worsen outcome. We therefore studied the relationship of plasma alcohol concentration with plasma dimethoate concentration and clinical outcome.

Materials and methods

Patients

Study patients were consecutive patients with dimethoate poisoning proven by analysis of plasma samples, admitted to the adult medical wards of three Sri Lankan hospitals, with alcohol assayed in the same plasma sample. They formed part of a cohort that has been previously published [10] and of a randomized controlled trial (RCT) that showed no effect of routine activated charcoal administration [11]. Ethics approval was obtained from the Oxfordshire Clinical Research Ethics Committee and Faculty of Medicine Ethics Committee, Colombo.

Patients were treated using a standard protocol [10]. Patients were resuscitated with fluids and atropine to raise

the systolic blood pressure above 80 mmHg, the heart rate above 80 bpm, and clear the lungs of audible secretions and wheeze. Pralidoxime chloride was administered 1 g every 6 h for 1–3 days.

Toxicological analysis

Blood samples were taken on admission from patients recruited to the RCT, before treatment with activated charcoal. Blood was immediately placed at 4°C, plasma extracted after centrifugation within 10 min, and samples stored at –23°C.

Dimethoate was determined in deproteinized plasma (trichloroacetic acid) by reversed-phase high-performance liquid chromatography with detection at 210 nm, using an acetonitrile-water eluent [12]. The precision of the determination of spiked blank plasma samples (100 µmol l⁻¹ dimethoate) carried through the whole procedure was $\pm 8\%$ [95% confidence interval (CI)]; the dimethoate concentration in patient plasma was calculated by comparison of peak areas. The sensitivity [lower limit of quantification (LOQ)] was 1 µmol l⁻¹. No details of the specificity can be given. However, when following the elimination kinetics of dimethoate in appropriate plasma samples, monoexponential kinetics was observed throughout, without indication of any plateau higher than the LOQ. From this we are confident that the determination was largely specific.

After absorption, dimethoate is converted to its oxon omethoate, which inhibits esterases including butyrylcholinesterase (BuChE). Reduced plasma BuChE activity is therefore a pharmacodynamic quantitative marker of exposure to dimethoate. We assayed BuChE activity in all samples as previously reported [13].

The alcohol determination was based on an enzymatic test using alcohol dehydrogenase (LOQ 0.05 g l⁻¹). The procedure used by the certified lab was validated according to legal medicine standards.

Statistics

Data analysis was performed in Stata v10 (StataCorp LP, College Station, TX, USA). Clinical characteristics were summarized using counts (percentages) for categorical variables and the median [interquartile range (IQR)] for non-normally distributed continuous variables. The Mann–Whitney test was used to compare group medians, and χ^2 tests and odds ratios (ORs) to compare categorical values. Nonparametric approaches were used to relate plasma dimethoate and alcohol concentrations. Multivariable logistic and linear regression models were used to investigate whether associations between (i) alcohol and mortality and (ii) alcohol and dimethoate levels were confounded by age or gender. In the linear regression models we transformed dimethoate levels using the square root transformation to improve the normality of its distribution.

Results

A paired plasma alcohol analysis was available for 72 patients [55 (76.4%) male] with dimethoate detected in plasma. The median time delay between dimethoate ingestion and blood sampling was 3 h (IQR 2–4 h). Thirty-seven patients (51.4%) had a detectable plasma alcohol concentration [$\geq 0.05 \text{ g l}^{-1}$ (5 mg dl^{-1})]. The median alcohol concentration for the 72 patients was 0.15 g l^{-1} (15 mg dl^{-1}) [IQR 0–1.15; maximum concentration 2.95 g l^{-1} (295 mg dl^{-1})]; for the 37 patients with detectable alcohol the median alcohol concentration was 1.10 g l^{-1} (110 mg dl^{-1}) (IQR 0.78–1.65).

Compared with patients with no alcohol in their blood, patients with detectable alcohol were more likely to be male [97.3% of those with alcohol detected were male compared with 54.3% of those without alcohol; χ^2 18.2 (1 d.f.), $P < 0.001$] and older [median age 39 years (IQR 33–45) vs. 25 years (IQR 20–32), Mann–Whitney $P < 0.001$].

The median plasma dimethoate concentration was higher in patients with alcohol detectable in their plasma on admission than in those with no alcohol [$479 \mu\text{mol l}^{-1}$ (IQR 268–701) vs. $145 \mu\text{mol l}^{-1}$ (IQR 25–337); Mann–Whitney $P < 0.001$; Figure 1]. Using nonparametric approaches, blood dimethoate concentrations were positively associated with blood alcohol (Spearman's $\rho = 0.34$; $P = 0.0032$). In linear regression models controlling for the study member's age, the association of alcohol with dimethoate differed in men and women [P (interaction) = 0.03]. In men, but not women, in age-adjusted models, alcohol was positively associated with dimethoate concentration ($P = 0.002$).

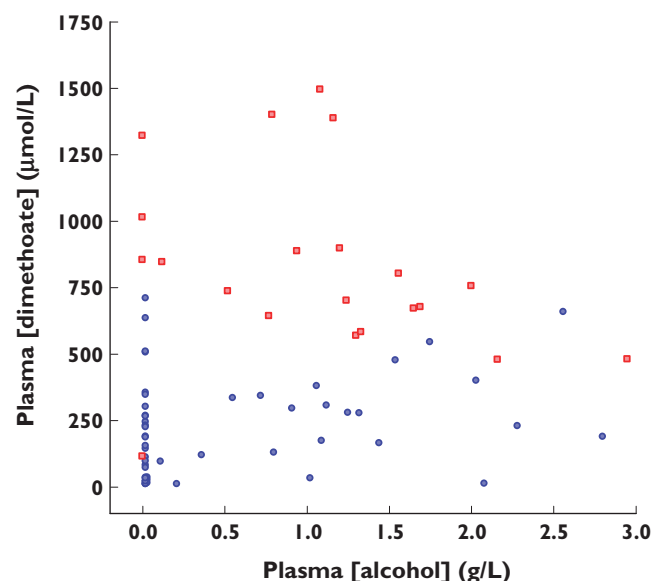


Figure 1

Relationship of plasma alcohol and dimethoate concentrations taken on admission in survivors (blue circles) and patients who died (red squares)

Median BuChE activity was slightly higher in patients with alcohol detectable on admission than in those with no alcohol detectable [1561 mU ml^{-1} (IQR 837–2829) vs. 1252 mU ml^{-1} (IQR 216–2829); Mann–Whitney $P = 0.20$; normal range $3000\text{--}6000 \text{ mU ml}^{-1}$]. No major difference was seen in median activity between patients with high concentrations of alcohol compared with those with low concentrations: 1529 mU ml^{-1} (IQR 837–3252) vs. 1737 mU ml^{-1} (IQR 547–2071) (Mann–Whitney $P = 0.65$). Using nonparametric approaches, BuChE activity was not associated with plasma alcohol concentration (Spearman $\rho = 0.165$; $P = 0.16$).

Twenty-one patients died (21/72, 29.2%). The median alcohol concentration in patients who died [0.94 g l^{-1} (94 mg dl^{-1}), IQR 0.52–1.30] was higher than the concentration in those who survived (0.0 g l^{-1} , IQR 0.00–1.04; Mann–Whitney $P = 0.018$). In logistic regression models controlling only for sex, the risk of death was four times higher in people who drank alcohol compared with those who did not (OR 4.3, 95% CI 1.2, 16.4). The OR remained significantly high when only men were studied (OR 4.8, 95% CI 1.2, 19.3); amongst women, there was only one death and she had not consumed alcohol.

In further logistic regression models controlling for age as well as sex, the risk of death associated with alcohol ingestion was weakened by controlling for age (OR 4.1, 95% CI 1.0, 17.8), but abolished by additionally controlling for dimethoate (OR 0.3, 95% CI 0.0, 8.8). This indicates that the deaths were not due to the direct toxic effects of alcohol. Controlling for the variation in delay between poison ingestion and blood sampling did not alter our findings.

Discussion

This study found that male patients with alcohol detectable in their blood had higher blood concentrations of dimethoate insecticide and increased mortality than patients with no alcohol in their blood. These results support the hypothesis that alcohol co-ingestion worsens outcome in dimethoate poisoning. The worse outcome is likely to result from larger ingestions of dimethoate and not from any dose-specific effect of alcohol (by, for example, increasing the risk of respiratory failure), since controlling for dimethoate in the analysis removed the effects of alcohol. The concentrations of plasma alcohol found in this study were not particularly high, supporting the conclusion that the alcohol ingestion is associated with altered behaviour (larger ingestions of dimethoate) and not direct toxic effects. This indicates that the treatment of alcohol intoxication is not relevant after acute dimethoate insecticide co-ingestion.

An alternative hypothesis is that alcohol alters the metabolism of dimethoate, slowing its elimination, thus raising its blood concentration. Slowed conversion of dimethoate to its active metabolite omethoate is sug-

gested by the lack of a substantial difference in BuChE inhibition (related to omethoate concentration) between patients ingesting and not ingesting alcohol, despite the higher concentrations of dimethoate in those with detectable alcohol. However, against this hypothesis, CYP3A4 dominates metabolism at high dimethoate concentrations [14] and there is little evidence that this enzyme is acutely inhibited by alcohol [15].

A limitation of this study is that we did not quantify chronic exposure to alcohol, a likely confounder [9] in understanding the relationship between acute alcohol use and OP poisoning. A second limitation is that we looked at only a single OP, dimethoate, which has differences in pharmacokinetics and dynamics, and clinical syndrome, compared with many other OPs [12]. However, some complicating features of acute alcohol exposure are likely to be relevant to any OP insecticide that causes early loss of consciousness and respiratory drive.

A third limitation is that the blood alcohol measurements were, of necessity, delayed compared with alcohol and insecticide ingestion. The T_{\max} of blood ethanol is about 100 min after oral ingestion, and may be prolonged by co-ingestants. Therefore the median 3-h delay to blood sampling will have underestimated the blood alcohol concentration (and moved some patients who had drunk small amounts into the no-alcohol group) if the alcohol was simultaneously ingested with the OP.

Larger studies are needed to assess more comprehensively the interaction of acute and chronic alcohol use on outcome in pesticide and other forms of poisoning, in both men and women. Such studies will ideally recruit patients with confirmed exposure to a range of OPs and assess chronic exposure to alcohol.

Conclusion

Coincident ingestion of alcohol increases the amount of dimethoate insecticide ingested for self-harm and thus the risk of death. Larger studies are required to assess this further, since efforts globally to reduce deaths from insecticide self-poisoning may benefit from concurrent efforts to reduce alcohol consumption.

Competing interests

None declared.

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